

## REMARKS

The specification has been amended in view of drawing changes which were made to place the informal drawings into accordance with Patent Office drafting regulations<sup>1</sup>. No new matter has been added by these amendments.

Claims 1, 4-34, 36, 45, 46, 86-90, 157-181, 183, 212, 213, 263-267 and 280-292 were pending in the application. In the Office Action dated July 1, 2003, claims 46, 88, 212, 213, 266 and 267 were withdrawn from consideration as belonging to a non-elected species, and claims 1, 4-34, 36, 45, 86, 87, 89, 90, 157-181, 183, 263-265 and 280-292 were rejected. In the instant Amendment, claims 1, 36, 183, 263 and 284-285 have been amended. These amendments are made to make the claim language clearer, and are not made to narrow the scope of the claims. Applicants submit that entry of the amendments presented herein is proper in that the amendments place the claims in condition for allowance or place the case in better condition for appeal. Upon entry of the above-made amendments, claims 1, 4-34, 36, 45, 46, 86-90, 157-181, 183, 212, 213, 263-267 and 280-292 will be pending.

Claim 1 has been amended to recite that in the method, for at least one gene in said plurality of different genes, said measuring comprises measuring the expression level of each of a plurality of different variants of an exon in said at least one gene. Claim 1 has also been amended to recite that each of said plurality of different variants is a form of said exon generated using a different 3' or 5' splice junction of said exon. Support for the amendment is found in the specification at page 9, lines 23-24; page 13, lines 17-27 and page 38, lines 10-25.

Claims 36 and 183 have been amended to make the claim language clearer by deleting the word "absolute." Support for the amendment is found in the specification at page 13, lines 13-17.

Claim 263 has been amended to recite that said array of polynucleotide probes comprises one or more sets of successive overlapping probes tiled along the longest variant

---

<sup>1</sup> In the Office Action Summary attached to the Office Action dated July 1, 2003, Box 10 b) and Box 11 a) are checked. Pursuant to a telephone conversation between Applicants' representative Weining Wang and Examiner Lu on October 30, 2003, there is no need to submit drawings with this response since these boxes were checked in error.

among said plurality of different variants of said exon. Support for the amendment is found in the specification at page 13, lines 20-27.

Claims 284 and 285 have been amended to make the claim language clearer by deleting the word “possible.” Support for the amendment is found in the specification at page 9, lines 23-24; page 13, lines 17-27 and page 38, lines 10-25. Claims 284 and 285 have also been amended to recite that each of said plurality of different variants is a form of said exon generated using a different 3' or 5' splice junction of said exon. Support for the amendment is found in the specification at page 13, lines 20-22.

No new matter has been added by these amendments. Entry of the foregoing amendments and consideration of the following remarks are respectfully requested.

#### APPLICANTS' INTERVIEW SUMMARY

Applicants thank Examiner Frank Lu, Ph.D., for the courtesies extended during the telephone interview on October 23, 2003 (hereinafter “the Interview”) with Applicants' representatives Adriane M. Antler, Weining Wang, and R. Douglas Bradley. During the interview, the claim rejections under 35 U.S.C. § 112, second paragraph, and the claim rejections under 35 U.S.C. § 102(e) and § 103(a) based on DeRisi et al., 1996, Nature Genetics 14:457-460 (“DeRisi”) and Friend et al., U.S. Patent No. 6,165,709 were also discussed.

With respect to the rejection under 35 U.S.C. § 112, second paragraph, stated in paragraph 5 of the instant Office Action, Dr. Antler directed the attention of the Examiner to page 13, lines 27-29, of the specification for a definition of the term “multiexon.” Dr. Antler explained that a multiexon refers to a nucleotide sequence spanning 2 or more neighboring exons and that a multiexon is a portion of the total exons present in an mRNA transcript of a gene. The Examiner indicated that the definition makes the term multiexon clear.

With respect to the rejection under 35 U.S.C. § 112, second paragraph, stated in paragraph 6 of the instant Office Action, Dr. Antler proposed to delete the term “absolute.” The Examiner indicated that the proposed claim amendment would obviate the rejection.

With respect to the rejection under 35 U.S.C. § 112, second paragraph, stated in paragraph 7 of the instant Office Action, Dr. Antler explained that the longest variant of an

exon refers to the variant that has the longest distance between its 3' and 5' end splice junctions. Dr. Antler directed the attention of the Examiner to page 13, lines 20-22 and lines 24-25, of the specification in connection therewith. The Examiner indicated that he would like to have claim 263 amended to recite that the longest variant is "among" the plurality of variants of the exon. Dr. Antler agreed to amend the claim accordingly.

With respect to the rejection under 35 U.S.C. § 112, second paragraph, stated in paragraph 8 of the instant Office Action, Dr. Antler directed the attention of the Examiner to page 13, lines 20-22 and lines 24-25, of the specification for the definition of a variant of an exon. Dr. Antler also directed the attention of the Examiner to FIG. 1 of the disclosure for an illustration of exons having different splice junctions, exon variants, and probes suitable for measuring the expression levels of the different exon variants. Dr. Antler explained that a variant of an exon is generated, e.g., by using one of the different 3' end splice junctions. The Examiner indicated that he wishes to review the disclosure again when the response is filed.

With respect to the rejections under 35 U.S.C. § 102(e) based on DeRisi and Friend, respectively, and the rejections under 35 U.S.C. § 103(a) based on DeRisi, Friend, and Friend in view of Chee, respectively, Dr. Antler proposed to amend the independent claims such that the term "possibly" (claim 1) or "possible" (claims 284 and 285) is deleted, and pointed out that none of the cited references teaches measuring the expression levels of different variants of an exon. Dr. Antler also pointed out that the Examiner indicated in the Office Action dated July 1, 2003 that the Examiner agrees with the Applicants that DeRisi or Friend does not teach distinguishing among different variants of an exon, and that the rejections were made because of the presence of the word "possibly" (claim 1) or "possible" (claims 284-285) (see, e.g., pages 6 and 13 of the instant Office Action). Dr. Antler pointed out that the proposed amendments would obviate the rejections. The Examiner indicated that the amendment as proposed would overcome the rejections based on these cited references.

Dr. Antler also requested that the Examiner review and initial the List of References Cited ("List") filed with the Supplemental Information Disclosure Statement on April 1, 2003. The Examiner indicated that he will review the references and forward the initialed List to Attorneys for Applicants.

THE OBJECTION TO THE SPECIFICATION SHOULD BE WITHDRAWN

The disclosure is objected to because of the informality that there is no description for Figure 4c. Applicants have amended the specification to include a description for Figure 4c. The objection is therefore obviated and should be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH SHOULD BE WITHDRAWN

Claims 1, 4-34, 36, 45, 86, 87, 89, 90, 157-181, 183, 263-265 and 280-292 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4-6, 11-12, 89, 90, 158 and 159 are rejected under 35 U.S.C. § 112, second paragraph, because of the phrase “individual multiexon.” The Examiner contends that it is unclear what “individual multiexon” means. Applicants respectfully point out that, as discussed during the Interview, a multiexon refers to a nucleotide sequence spanning 2 or more neighboring exons that are a portion of the total exons present in an mRNA transcript for the corresponding gene (see specification page 13, lines 27-29). Therefore, the meaning of “individual multiexon” is clear, and the rejection should be withdrawn.

Claims 36 and 183 are rejected under 35 U.S.C. § 112, second paragraph, because of the phrase “wherein said expression levels are measured as absolute abundance.” The Examiner contends that it is unclear how absolute abundance can be directly measured. Applicants have amended the claims to delete the term “absolute.” The rejection is therefore obviated and should be withdrawn.

Claim 263 is rejected under 35 U.S.C. § 112, second paragraph, because of the phrase “the longest variant of an exon.” Applicants respectfully direct the attention of the Examiner to the specification at page 13, lines 20-27, for a definition of a variant of an exon and disclosures regarding the length of such a variant. It is therefore clear that the length of an exon variant is the distance between the 3' and 5' end splice junctions of the exon variant. Thus, the longest variant of an exon refers to the variant of the exon which spans the nucleotide sequence between the 3' and 5' end splice junctions which are located the farthest apart from each other relative to the distance between the 3' and 5' end splice junctions of

other variants of the exon. Pursuant to the suggestion of the Examiner at the Interview, Applicants have amended claim 263 to recite that the array of polynucleotide probes comprises one or more sets of successive overlapping probes tiled along the longest variant *among said* plurality of different variants. The rejection should therefore be withdrawn.

Claims 284 and 285 are rejected under 35 U.S.C. § 112, second paragraph, because of the phrase “each of said variants being a form of said exon generated using a different splice junction of said exon.” Applicants respectfully submit that, as illustrated in FIG. 1 of the disclosure, an exon (e.g., exon 3 and exon 4 in FIG. 1) may have several alternative 5' or 3' splice junctions. A variant of an exon is a form of the exon generated using one of such alternative splice junctions. Applicants have amended the claims to recite that each of said plurality of different variants being a form of said exon generated using a different 3' or 5' splice junction of said exon. Thus, the rejection of claims 284 and 285 should be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

Claims 1, 4-6 and 45 are rejected under 35 U.S.C. § 102(e) as being anticipated by DeRisi et al., 1996, Nature Genetics 14:457-460 (“DeRisi”)<sup>2</sup>. Claims 1, 10-12, 22-26, 28-33, 45, 86, 87, 89, 90, 157-159, 169-173, 175-180, 265, and 280-282 are rejected under 35 U.S.C. § 102(e) as being anticipated by Friend et al., U.S. Patent No. 6,165,709 (“Friend”). Applicants respectfully disagree with the Examiner for the reasons presented below.

A claim is anticipated under 35 U.S.C. § 102 only if each and every element and limitation as set forth in the claim is found, either expressly described or inherently present, in a single prior art reference. *Glaxo, Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047 (Fed. Cir. 1995). There must be *no differences* between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Fdn. v. Genentech, Inc.* 927 F. 2d. 1565, 1576 (Fed. Cir. 1991). Anticipation requires that all aspects of the claimed invention were already described in a *single* reference. *Scripps Clinic & Research Fdn. v. Genentech, Inc.* 927 F. 2d. 1565, 1576 (Fed. Cir. 1991).

---

<sup>2</sup> Applicants respectfully point out that the rejection based on DeRisi should be made under 35 U.S.C. § 102(b), rather than 35 U.S.C. § 102(e). However, the arguments presented herein are not affected by this error.

Claims 1, 4-6 and 45 are rejected under 35 U.S.C. § 102(e) as being anticipated by DeRisi. DeRisi teaches determining the relative expression levels of 870 different genes in two cell samples, a tumorigenic cell line and a non-tumorigenic cell line, by measuring the hybridization levels of mRNAs corresponding to each genes using a DNA microarray containing 870 different cDNAs. Thus, in DeRisi, the expression level of an entire mRNA transcribed from a gene is measured by a cDNA clone on its microarray. Applicants respectfully point out that DeRisi does not teach measuring the expression levels of each of a plurality of variants of an exon. Therefore, Applicants respectfully submit that DeRisi does not anticipate claims 1, 4-6 and 45, and that the rejection under 37 C.F.R. § 102(e) based on DeRisi should be withdrawn.

Claims 1, 10-12, 22-26, 28-33, 45, 86, 87, 89, 90, 157-159, 169-173, 175-180, 265, and 280-282 are rejected under 35 U.S.C. § 102(e) as being anticipated by Friend. Friend teaches methods for identifying targets of a drug in a cell. Friend teaches that the expression levels of a plurality of genes in a cell sample can be measured using a DNA array containing one or more binding sites for the mRNA transcribed from each gene. Applicants respectfully point out that Friend does not teach measuring the expression levels of each of a plurality of variants of an exon. Therefore, Applicants respectfully submit that Friend does not anticipate claims 1, 10-12, 22-26, 28-33, 45, 86, 87, 89, 90, 157-159, 169-173, 175-180, 265, and 280-282, and that the rejection under 37 C.F.R. § 102(e) based on Friend should be withdrawn.

#### THE REJECTIONS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 8 and 9 are rejected under 35 U.S.C. § 103(a) as being unpatentable over DeRisi et al., 1996, Nature Genetics 14:457-460 ("DeRisi"). Claims 27, 174 and 284 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Friend et al., U.S. Patent No. 6,165,709 ("Friend"). Claims 13-21 and 160-168 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Friend in view of Chee et al., U.S. Patent No. 6,355,431 ("Chee"). Applicants respectfully disagree with the Examiner for the reasons presented below.

A finding of obviousness under 35 U.S.C. § 103(a) requires a determination that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383, U.S. 1 (1956). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in

the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

With respect to the rejection of claims 8 and 9, the Examiner contends that DeRisi renders these claims unpatentable in that DeRisi teaches the limitations of base claims 1 and 4-7, and that it would have been obvious to one of skilled in the art to have measured the expression levels of 1,000-10,000 different genes. As discussed above, DeRisi does not teach or suggest measuring the expression levels of each of a plurality of variants of an exon. Thus, Applicants respectfully submit that DeRisi does not render obvious claims 8 and 9 of the presently claimed invention irrespective of whether it would have been obvious to one of skilled in the art to have measured the expression levels of 1,000-10,000 different genes.

With respect to the rejection of claims 27, and 174, the Examiner contends that Friend renders these claims unpatentable in that Friend teaches the limitations of the respective base claims and that it would have been obvious to one of skilled in the art to immobilize different length of polynucleotide probes on an array. As discussed above, Friend does not teach or suggest measuring the expression levels of each of a plurality of variants of an exon. Thus, Applicants respectfully submit that Friend does not render obvious claims 27 and 174 of the presently claimed invention irrespective of whether it would have been obvious to one of skilled in the art to immobilize different lengths of polynucleotide probes on an array.

With respect to claim 284, Applicants respectfully point out that they believe claim 284 to be incorrectly included in this rejection since claim 284 does not contain a limitation regarding the length of polynucleotide probes on the array. Nevertheless, Friend also does not render claim 284 obvious, since Friend does not teach or suggest using variant junction probes for each of a plurality of different variants of an exon.

With respect to the rejection of claims 13-21 and 160-168, the Examiner contends that Friend in view of Chee renders these claims unpatentable in that Friend teaches the limitations of the respective base claims and that Chee teaches the limitations recited in claims 13-21 and 160-168. As discussed above, Friend does not teach or suggest measuring the expression levels of each of a plurality of variants of an exon. Chee teaches compositions and methods for detecting and quantifying a target nucleic acid using a variety of both signal amplification and target amplification techniques. Chee does not provide what is missing in

Friend. Thus, Applicants respectfully submit that Friend in view of Chee does not render obvious claims 13-21 and 160-168 of the presently claimed invention.

Therefore, Applicants respectfully submit that the rejection of claims 8, 9, 13-21, 27, and 160-168 under 37 C.F.R. § 103 (a) should be withdrawn.

CLAIMS WITHDRAWN FROM CONSIDERATION AS BELONGING TO NON-ELECTED SPECIES SHOULD BE CONSIDERED

Claims 46, 88, 212, 213, 266 and 267 were withdrawn from consideration by the Examiner as belonging to a non-elected species. Since Applicants believe that the generic claims are allowable, claims 46, 88, 212, 213, 266 and 267 should be considered by the Examiner. Applicants respectfully request that these claims be considered by the Examiner.

LIST OF REFERENCES CITED FILED ON APRIL 1, 2003

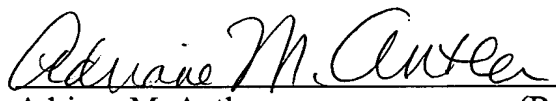
Applicants respectfully request that the Examiner forward to Attorneys for Applicants a copy of the List of References Cited filed on April 1, 2003, initialed by the Examiner to indicate his consideration of the references cited therein.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Applicants believe that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application are respectfully requested.

Respectfully submitted,

Date: November 3, 2003

 32,605  
Adriane M. Antler (Reg. No.)  
PENNIE & EDMONDS LLP  
1155 Avenue of the Americas  
New York, New York 10036-2711  
(212) 790-9090